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PCT

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Attorney's Docket Number 48498-258443

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. Application No. (if known, see 37 CFR 1.5) 09/856681

International Application No.	International Filing Date	Priority Date Claimed
PCT/EP99/09215	26 November 1999 (26.11.1999)	26 November 1998 (26.11.1998)

Title of Invention

HUMAN SEMAPHORIN 6A-1 (SEMA6A-A), A GENE INVOLVED IN NEURONAL DEVELOPMENT AND REGENERATION MECHANISMS DURING APOPTOSIS, AND ITS USE AS A POTENTIAL DRUG TARGET

Applicant(s) for DO/EO/US

BEHL, Christian; KLOSTERMANN, Andreas

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information: return postcard

U.S. Application No. (if known, see 37 CFR 1.5)	International Application No.	Attorney's Docket Number
09/856681	PCT/EP99/09215	48498-258443

17. ☒ The following fees are submitted: CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $970.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $840.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... $760.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) $670.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) $96.00

ENTER APPROPRIATE BASIC FEE AMOUNT =				$840	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$130	
Claims	Number Filed	Number Extra	Rate		
Total claims	1 - 20 =	0	x 18.00	$	
Independent Claims	1 - 3 =	0	x 78.00	$	
Multiple Dependent Claims (if applicable)			+ 260.00	$	
TOTAL OF ABOVE CALCULATIONS =				$970	
Reduction of 1/2 for filing by small entity, if applicable. Applicant claims small entity status. -				$485	
SUBTOTAL =				$485	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$485	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$	
TOTAL FEES ENCLOSED =				$485	
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $485 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 11-0855 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 11-0855. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
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Patents

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

BEHL, CHRISTIAN et al.

Serial No.: **Filed Concurrently Herewith, U. S. National Phase of PCT EP 99/09215 Filed November 26, 1999**

Filed: **May 22, 2001**

For: **HUMAN SEMAPHORIN 6A-1 (SEMA6A-A), A GENE INVOLVED IN NEURONAL DEVELOPMENT AND REGENERATION MECHANISMS DURING APOPTOSIS, AND ITS USE AS A POTENTIAL DRUG TARGET**

PRELIMINARY AMENDMENT

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination of the concurrently filed patent application, please make the following amendments.

In The Specification:

I hereby certify that this correspondence is being deposited with the United States Postal Service as **Express Mail No. EL329505255US** addressed to: Assistant Commissioner of Patents, Box Patent Application, Washington, DC, 20231, on May 22, 2001.

John K. McDonald, Ph.D. - Reg. No. 42,860

Please amend the specification as follows:

On page 1, after the title "Human Semaphorin 6A-1 (SEMA6A-A), A Gene Involved in Neuronal Development and Regeneration Mechanisms During Apoptosis, and Its Use as a Potential Drug Target", please add the following:

Prior Related Applications

This application is the U. S. National Phase filing of International Application PCT/EP99/09215, with an international filing date of November 26, 1999, which claims priority to European Patent Application No. 98 122 441.3 filed November 26, 1998.

In The Claims:

Prior to examination of the application, please cancel Claims 1-21 and add the following new claim.

22. (New) Nucleic acid coding for human semaphorin 6A-1 comprising:

(a) the nucleotide sequence shown in SEQ ID NO: 1,

(b) a sequence corresponding to the nucleotide sequence shown in SEQ ID NO: 1 within the degeneration of the genetic code,

or

(c) a sequence which hybridizes with the sequences of (a) or/and

(b) under stringent conditions

with the proviso that it contains a nucleic acid coding for a binding domain of human semaphorin 6A-1 comprising:

(d) the nucleotide sequence shown in SEQ ID NO:3,

(e) a sequence corresponding to the nucleotide sequence shown in SEQ ID NO:3 within the degeneration of the genetic code, or

(f) a sequence which hybridizes with the sequences of (d) or/and (e) under stringent conditions.

No additional fees are believed due; however, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 11-0855.

Respectfully submitted,

John K. McDonald, Ph.D.
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HUMAN SEMAPHORIN GA-1 (SEMAGA-A), A GENE INVOLVED IN NEURONAL DEVELOPMENT AND REGENERATION MECHANISMS DURING ADOPTOSIS, AND ITS USE AS A POTENTIAL DRUG TARGET

Specification

The present invention relates to human semaphorin 6A-1 (SEMA6A-1), a novel gene involved in neuronal development and regeneration mechanisms during apoptosis.

Actin binding and filament assembly controlling proteins are essential for cellular events that require a drastic remodelling of cytoskeletal elements during development and apoptosis. Proline-rich proteins of the Ena/VASP family play a crucial role in actin and filament dynamics and have only recently been shown to be clustered to cell surface receptors like Dlar, a tyrosine phosphatase essential for motor axon outgrowth (F.B.Gertler et al., 1996, Cell 87, 227-239; Z.Wills et al., 1999, Neuron 22, 301-312). In the last decade the semaphorins were identified as a protein family displaying secreted or transmembrane-based repulsive guidance cues critically involved in neuronal development (J.G.Culotti and A.L.Kolodkin, Curr.Op.Neurobiol., 6, 81-88).

Therefore, it was an object of the present invention to provide a novel human semaphorin variant.

The invention comprises a nucleic acid coding for human semaphorin 6A-1 comprising

(a) the nucleotide sequence shown in SEQ ID NO:1,

(b) a sequence corresponding to the nucleotide sequence shown in SEQ ID NO:1 within the degeneration of the genetic code, or

(c) a sequence which hybridizes with the sequences of (a) or/and (b) under stringent conditions.

Surprisingly, the transmembranous human semaphorin 6A-1 ((HSA) SEMA6A-1) is capable of a selective binding to members of the Ena/VASP protein family. (HSA)SEMA6A-1 contains a cytoplasmic stretch at its C-terminal end. This domain shares a striking homology to Zyxin, a protein known to bind Ena/VASP (T.Macalma et al., 1996, JBC 271, 31470-31478; S.Hu and L.F.Reichardt, Neuron 22, 419-422). Thus, the human semaphorin sequence was found to comprise a section which matches with other semaphorin sequences, e.g. murine semaphorin sequences as well as a novel domain at its C-terminal end which is capable of binding to elements attached to the cytoskeleton.

Therefore, the invention further comprises a nucleic acid coding for a binding domain of human semaphorin 6A-1 comprising: (a) the nucleotide sequence shown in SEQ ID NO:3,(b) a sequence corresponding to the nucleotide sequence shown in SEQ ID NO:3 within the degeneration of the genetic code, or (c) a sequence which hybridizes with the sequences of (a) or/and (b) under stringent conditions.

The term "hybridization under stringent conditions" according to the present invention is used as described by Sambrook et al. (Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press (1989), 1.101-1.104). Preferably, a stringent hybridization according to the present invention is given when after washing for an hour with 1 x SSC and 0.1% SDS at 50°C, preferably at 55°C, more preferably at 62°C, and most preferably at 68°C, and more preferably for 1 hour with 0.2 x SSC and 0.1% SDS at 50°C, preferably at 55°C, more preferably at 62°C, and most preferably at 68°C a positive hybridization signal is still observed. A nucleotide sequence which hybridizes under such washing conditions with the nucleotide sequence shown in SEQ ID NO:1 or with a nucleotide

sequence corresponding thereto within the degeneration of the genetic code is a nucleotide sequence according to the invention.

The nucleic acid according to the invention preferably is in operative association with an expression control sequence that is active in eukaroytic cells, preferably in mammal cells.

The nucleotide sequence according to the invention preferably is a DNA. However, it may also be an RNA or a nucleic acid analog, such as a peptidic nucleic acid.

The nucleic acid according to the invention preferably comprises a sequence having a homology of greater than 80%, preferably greater than 90%, and more preferably greater than 95% and, in particular, greater than 97% to the nucleotide sequence according to SEQ ID NO:1. The term homology as used herein can be defined by the equation $H(\%) = [1-V/X] \cdot 100$, wherein H means homology, X is the total number of nucleobases of the nucleotide sequence according to SEQ ID NO:1 and V is the number of different nucleobases of a comparative sequence with regard to the nucleotide sequence according to SEQ ID NO:1.

The invention further comprises a polypeptide encoded by a nucleic acid according to the invention. Such a polypeptide is, in particular, capable of binding to members of the Ena/VASP protein family. The transmembranous SEMA6A-1 is capable of selectively binding to Evl but not Mena, both members of the Ena/VASP protein family.

The nucleic acids according to the invention can be obtained using known techniques, e.g. using short sections of the nucleotide sequence shown in SEQ ID NO:1 as hybridization probe or/and primer. They can, however, also be produced by chemical synthesis.

The invention further comprises a recombinant vector containing at least one copy of the nucleic acid according to the invention. This vector may be a prokaryotic or a eukaryotic vector which contains the nucleic acid according to the invention under the control of an expression signal (promoter, operator, enhancer etc.). Examples of prokaryotic vectors are chromosomal vectors such as bacteriophages and extra-chromosomal vectors such as plasmids, circulary plasmid vectors being particularly preferred. Prokaryotic vectors useful according to the present invention are, e.g., described in Sambrook et al., supra, chapter 1-4.

More preferably, the vector according to the invention is a eukaryotic vector, in particular a vector for mammal cells. Most preferred are vectors suitable for gene therapy, such as retrovirus, modified adenovirus or adeno-associated virus. Such vectors are known to the man skilled in the art of molecular biology and gene therapy and are also described in Sambrook et al., supra, chapter 16.

In addition to the polypeptide encoded by the nucleic acid of SEQ ID NO:1 or SEQ ID NO:3, the invention also relates to polypeptides differing therefrom by substitutions, deletions or/and insertions of single amino acids or short amino acid sections. The polypeptide is obtainable by expression of the nucleic acid sequence in a suitable expression system (cf. Sambrook et al., supra).

The polypeptide encoded by SEQ ID NO:1 is (HSA)SEMA6A-1, a new semaphorin variant containing a Zyxin-like domain that binds to the Ena/VASP-like protein (Evl). In particular, the semaphorins are a protein family displaying secreted or transmembrane-based repulsive guidance cues critically involved in neuronal development. The polypeptide encoded by SEQ ID NO:3 is a binding domain. This domain can bind selectively to Evl, a member of the Ena/VASP protein family. It may be particularly favorable to combine this binding domain with other proteins having known

functionality to give a fusion protein. This binding domain can be used advantageously, alone or as part of a fusion protein, as a means for screening and as a diagnostic and therapeutic target.

The invention further comprises a cell transformed with a nucleic acid or a vector according to the invention. The cell may be a eukaryotic or a prokaryotic cell, eukaryotic cells being preferred.

The present invention also comprises the use of the polypeptide or fragments thereof as immunogen for the production of antibodies. Standard protocols for obtaining antibodies may be used.

The present invention also comprises a pharmaceutical composition comprising a nucleic acid, modified nucleic acid, vector, cell, polypeptide or antibody as defined herein as active component.

The pharmaceutical composition may comprise pharmaceutically acceptable carriers, vehicles and/or additives and additional active components, if desired. The pharmaceutical composition can be used for diagnostic purposes or for the production of therapeutic agents. Particularly preferred is the use as a therapeutic agent for the modulation of the immune system.

Since the human semaphorin 6A-1 gene is involved in neuronal development and regeneration mechanisms during apoptosis, this gene can be used to design drug target structures. Members of the semaphorin gene family act as guidance signals and regulatory molecules during neuronal development. Besides its role in development, semaphorin has essential functions in the immune system. Semaphorin can also be linked to potential cancer, drug resistance and disease genes.

On the basis of a phylogenetic approach, the semaphorin gene family is currently distinguished into eight classes containing invertebrate (classes 1,

2) and vertebrate proteins (classes 3-7). Consistent with this nomenclature, the newly identified semaphorin is grouped into class 6 as human semaphorin 6A-1.

RNA expression studies have revealed SEMA6A-1 expression in areas consistent with a role of SEMA6A-1 as a guidance and regulatory signal during development and regeneration. Specialized domains in the cytoplasmic tail of the SEMA6A-1 gene product containing cytoskeletal binding elements show that SEMA6A-1 is also involved in differentiation, cytoskeletal stabilization and plasticity.

Finally, the invention is also directed to the use of the herein described pharmaceutical compositions for effecting differentiation, cytoskeletal stabilization and/or plasticity.

The invention is further described by the appended figures and examples, wherein

Figure 1 shows SEQ ID NO:1, the coding nucleotide sequence of the human semaphorin 6A-1 gene.

Figure 2 shows the nucleotide sequence of the human semaphorin 6A-1 gene as well as the derived amino acid sequence thereof;

Figure 3 shows the tissue distribution of (HSA)SEMA6A-1 revealed by Northern blot hybridizations of human embryo brain, lung, liver, kidney and human adult heart, brain, placenta, lung, liver, skeletal muscle, kidney and pancreas tissue, respectively;

Figure 4 shows the (MMU)Sema6A-1 distribution in mouse adult and embryonic tissues revealed by in-situ hybridizations;

Figure 5 shows expression, protein size and dimerization of (HSA)SEMA6A-1;

Figure 6 shows a sequence alignment between SEMA6A-1 and Zyxin, wherein Figure 6a shows SEQ ID NO:3, the coding nucleotide sequence to a binding domain and Figure 6b shows the sequence of Zyxin;

Figure 7 shows immunoprecipitation of (HSA)SEMA6A-1 with α-Evl and α-Mena antibodies. A (α-Evl): Vector only (lane 1), pFlagSEMA6A-1 (lane 2), HT22 supplemented with purified SEMA6A-1 protein (lane 3), pFlagSEMA6A-1 precipitation using only protein A beads (lane 4), control detection of pFlagSEMA6A-1 transfected cells (lane 5), SEMA6A-1 purified control (lane 6), untransfected HT22 control (lane 7), Evl control in HT22 (lane 8); B (α-Mena): Vector only (lane 1), pFlagSEMA6A-1 (lane 2), HT22 supplemented with purified SEMA6A-1 protein (lane 3), control detection of pFlagSEMA6A-1 transfected cells (lane 4);

Figure 8 gives a graphical overview on the known Ena/VASP interacting proteins like Zyxin, Dlar and (HSA)SEMA6A-1.

Examples

Example 1

Cloning, genomic localization and tissue distribution of (HSA)SEMA6A-1

To identify and isolate repulsive guidance cues that might be involved in neuronal apoptosis a low stringency PCR-approach on cDNA from the human neuroblastoma cell line SK-N-MC was performed and a fragment of (HSA)SEMA6A-1 was amplified. This fragment was used to screen a human

1-ZAP Express cDNA library. Sequencing of 4 isolated clones revealed an ORF of 3093 bp referring to a protein of 1030 amino acids in total length with a predicted size of 135 kDa. (Fig.2: Nucleic acid sequence and deduced amino acid sequence).

Database searches identified 43 unordered sequences (Genbank Acc.-No. AC008524) and a mapped genomic survey sequence (Genbank Acc.-No. AB002453) of human chromosome 5 localizing the gene to 5q21-22. Gaps between the genomic sequences were closed by PCR on human genomic DNA and subsequent sequencing.

The (hsa)sema6A-1 gene covers 45 kb of genomic sequence and consists of 18 exons including 1 untranslated exon at the 3'-end (see Figure 2).

Example 2

Similarity and domain structure of (HSA)SEMA6A-1

Database searches revealed that SEMA6A-1 (1030aa) has a relatively high similarity to its murine ortholog Sema6A-1 (869aa) within the overlapping region consisting of 869aa. The existence of an additional cytoplasmic domain prompted us to name the new protein SEMA6A-1. This unique domain shares a 33% identity (49% similarity) to Zyxin, a proline-rich protein present at focal adhesion points and capable of binding to members of the Ena/VASP family. Binding of Zyxin to Ena/VASP occurs via a peptide stretch displaying the sequence DFPPPP (K.E.Prehoda et al., 1999, Cell 97, 471-480). (HSA)SEMA6A-1 contains two potential binding motifs (aa 858-962 (DNPPP) and aa 1010-1015 (DVPPKP) in its Zyxin homologous domain that are similar to the above-mentioned motif.

Example 3

Tissue distribution of (HSA)SEMA6A-1 revealed by Northern blot and in situ hybridization

Northern blot hybridizations of poly A^+ RNA of human adult and embryonic tissues detected two transcripts in the molecular range of 4.5 kb and 7 kb. Highest levels of detection were present in embryonic brain and kidney, moderate expression in lung and virtually no expression in liver. Compared to embryonic levels there was observed a clear reduction of expression of (HSA)SEMA6A-1 in adult tissues with the exception of placenta. In situ hybridizations in mouse embryo revealed a distinct expression throughout the whole embryo that is restricted to nervous system areas. These results indicate a general role of this protein in development and are shown in Figures 3 and 4: Figure 3 shows the human Northern blots. Figure 4 displays in situ hybridizations of embryonic (A, B, C, D) and adult (E, F, G) tissues. Notify the dominant expression in embryonic brain stem (A, B, D), optic precursors (A, C), spinal cord (B, D) and limb (B). High expression levels in adult regions are maintained in piriform cortex (E), cerebellar regions (F, G) and olfactory bulb (G).

Example 4

Expression of (HSA)SEMA6A-1 in mammalian cell lines

In order to show that Ena/VASP proteins might be potential intracellular binding partners for (HSA)SEMA6A-1 (see Figure 6, Alignment of (HSA)SEMA6A-1 and Zyxin) and that (HSA)SEMA6A-1 and Ena/VASP-like proteins might be interacting partners a XbaI/ScaI fragment of the SEMA6A-1 clone covering the full length protein sequence only lacking the signal sequence was subcloned into the pFLAG-CMV-1 vector. This vector allows rapid detection of the expressed fusion protein through the N-terminal Flag-Taq fused to the protein.

Immunoblotting of the tagged protein (Flag-SEMA6A-1) displayed a protein size of 125 kDa which closely corresponds to the predicted protein size. Expression in a human cell line (HEK293) and in a clonal mouse hippocampal cell line (HT22) followed by immunofluorescent analysis revealed that SEMA6A-1 is targeted to the cell surface and colocalizes with Evl and Mena, indicating a possible interaction between these proteins (see Figure 5, showing a graphical overview on the domain structure of (HSA)SEMA6A-1 and the subcloning strategy. In addition, Western blots displaying the protein size and its dimerization abilities are shown).

Example 5

Immunoprecipitation of (HSA)SEMA6A-1

Using antibodies specific for Mena and Evl Flag-SEMA6A-1 was immunoprecipitated from Triton X-100 extracts of transfected HEK239 and HT22 cells. The precipitate was separated by SDS-PAGE, and subsequent immunoblotting with the monoclonal anti-Flag antibody revealed that Flag-SEMA6A-1 co-immunoprecipitates with Evl but not Mena. To confirm this interaction Flag-SEMA6A-1 was purified from transfected HEK293 cells on an anti-Flag affinity column and the Triton X-100 extract of untransfected HT22 cells was supplemented with the purified protein, followed by immunoprecipiation of the protein complex using the α-Evl antibody. Immunoblotting again revealed that FlagSEMA6A-1 co-precipitates Evl. Figure 7 shows the immunoprecipitation experiments using the α-Evl- and α-Mena antibodies.

SEQUENCE LISTING

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Cys Ala Gly Ser Ser Ser Leu Glu Arg Tyr Ala Thr Ser Asn Glu Phe
    370                 375                 380

cct gat gat acc ctg aac ttc atc aag acg cac ccg ctc atg gat gag   1200
Pro Asp Asp Thr Leu Asn Phe Ile Lys Thr His Pro Leu Met Asp Glu
385                 390                 395                 400

gca gtg ccc tcc atc ttc aac agg cca tgg ttc ctg aga aca atg gtc   1248
Ala Val Pro Ser Ile Phe Asn Arg Pro Trp Phe Leu Arg Thr Met Val
                405                 410                 415

aga tac cgc ctt acc aaa att gca gtg gac aca gct gct ggg cca tat   1296
Arg Tyr Arg Leu Thr Lys Ile Ala Val Asp Thr Ala Ala Gly Pro Tyr
            420                 425                 430

cag aat cac act gtg gtt ttt ctg gga tca gag aag gga atc atc ttg   1344
Gln Asn His Thr Val Val Phe Leu Gly Ser Glu Lys Gly Ile Ile Leu
        435                 440                 445

aag ttt ttg gcc aga ata gga aat agt ggt ttt cta aat gac agc ctt   1392
Lys Phe Leu Ala Arg Ile Gly Asn Ser Gly Phe Leu Asn Asp Ser Leu
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    450                 455                 460

ttc ctg gag gag atg agt gtt tac aac tct gaa aaa tgc agc tat gat   1440
Phe Leu Glu Glu Met Ser Val Tyr Asn Ser Glu Lys Cys Ser Tyr Asp
465                 470                 475                 480

gga gtc gaa gac aaa agg atc atg ggc atg cag ctg gac aga gca agc   1488
Gly Val Glu Asp Lys Arg Ile Met Gly Met Gln Leu Asp Arg Ala Ser
                485                 490                 495

agc tct ctg tat gtt gcg ttc tct acc tgt gtg ata aag gtt ccc ctt   1536
Ser Ser Leu Tyr Val Ala Phe Ser Thr Cys Val Ile Lys Val Pro Leu
            500                 505                 510

ggc cgg tgt gaa cga cat ggg aag tgt aaa aaa acc tgt att gcc tcc   1584
Gly Arg Cys Glu Arg His Gly Lys Cys Lys Lys Thr Cys Ile Ala Ser
        515                 520                 525

aga gac cca tat tgt gga tgg ata aag gaa ggt ggt gcc tgc agc cat   1632
Arg Asp Pro Tyr Cys Gly Trp Ile Lys Glu Gly Gly Ala Cys Ser His
    530                 535                 540

tta tca ccc aac agc aga ctg act ttt gag cag gac ata gag cgt ggc   1680
Leu Ser Pro Asn Ser Arg Leu Thr Phe Glu Gln Asp Ile Glu Arg Gly
545                 550                 555                 560

aat aca gat ggt ctg ggg gac tgt cac aat tcc ttt gtg gca ctg aat   1728
Asn Thr Asp Gly Leu Gly Asp Cys His Asn Ser Phe Val Ala Leu Asn
                565                 570                 575

ggg cat tcc agt tcc ctc ttg ccc agc aca acc aca tca gat tcg acg   1776
Gly His Ser Ser Ser Leu Leu Pro Ser Thr Thr Thr Ser Asp Ser Thr
            580                 585                 590

gct caa gag ggg tat gag tct agg gga gga atg ctg gac tgg aag cat   1824
Ala Gln Glu Gly Tyr Glu Ser Arg Gly Gly Met Leu Asp Trp Lys His
        595                 600                 605

ctg ctt gac tca cct gac agc aca gac cct ttg ggg gca gtg tct tcc   1872
Leu Leu Asp Ser Pro Asp Ser Thr Asp Pro Leu Gly Ala Val Ser Ser
    610                 615                 620

cat aat cac caa gac aag aag gga gtg att cgg gaa agt tac ctc aaa   1920
His Asn His Gln Asp Lys Lys Gly Val Ile Arg Glu Ser Tyr Leu Lys
625                 630                 635                 640

ggc cac gac cag ctg gtt ccc gtc acc ctc ttg gcc att gca gtc atc   1968
Gly His Asp Gln Leu Val Pro Val Thr Leu Leu Ala Ile Ala Val Ile
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645 650 655

ctg gct ttc gtc atg ggg gcc gtc ttc tcg ggc atc acc gtc tac tgc 2016
Leu Ala Phe Val Met Gly Ala Val Phe Ser Gly Ile Thr Val Tyr Cys
660 665 670

gtc tgt gat cat cgg cgc aaa gac gtg gct gtg gtg cag cgc aag gag 2064
Val Cys Asp His Arg Arg Lys Asp Val Ala Val Val Gln Arg Lys Glu
675 680 685

aag gag ctc acc cac tcg cgc cgg ggc tcc atg agc agc gtc acc aag 2112
Lys Glu Leu Thr His Ser Arg Arg Gly Ser Met Ser Ser Val Thr Lys
690 695 700

ctc agc ggc ctc ttt ggg gac act caa tcc aaa gac cca aag ccg gag 2160
Leu Ser Gly Leu Phe Gly Asp Thr Gln Ser Lys Asp Pro Lys Pro Glu
705 710 715 720

gcc atc ctc acg cca ctc atg cac aac ggc aag ctc gcc act ccc ggc 2208
Ala Ile Leu Thr Pro Leu Met His Asn Gly Lys Leu Ala Thr Pro Gly
725 730 735

aac acg gcc aag atg ctc att aaa gca gac cag cac cac ctg gac ctg 2256
Asn Thr Ala Lys Met Leu Ile Lys Ala Asp Gln His His Leu Asp Leu
740 745 750

acg gcc ctc ccc acc cca gag tca acc cca acg ctg cag cag aag cgg 2304
Thr Ala Leu Pro Thr Pro Glu Ser Thr Pro Thr Leu Gln Gln Lys Arg
755 760 765

aag ccc agc cgc ggc agc cgc gag tgg gag agg aac cag aac ctc atc 2352
Lys Pro Ser Arg Gly Ser Arg Glu Trp Glu Arg Asn Gln Asn Leu Ile
770 775 780

aat gcc tgc aca aag gac atg ccc ccc atg ggc tcc cct gtg att ccc 2400
Asn Ala Cys Thr Lys Asp Met Pro Pro Met Gly Ser Pro Val Ile Pro
785 790 795 800

acg gac ctg ccc ctg cgg gcc tcc ccc agc cac atc ccc agc gtg gtg 2448
Thr Asp Leu Pro Leu Arg Ala Ser Pro Ser His Ile Pro Ser Val Val
805 810 815

gtc ctg ccc atc acg cag cag ggc tac cag cat gag tac gtg gac cag 2496
Val Leu Pro Ile Thr Gln Gln Gly Tyr Gln His Glu Tyr Val Asp Gln
820 825 830

ccc aaa atg agc gag gtg gcc cag atg gcg ctg gag gac cag gcc gcc 2544
Pro Lys Met Ser Glu Val Ala Gln Met Ala Leu Glu Asp Gln Ala Ala

835 840 845

aca ctg gag tat aag acc atc aag gaa cat ctc agc agc aag agt ccc 2592
Thr Leu Glu Tyr Lys Thr Ile Lys Glu His Leu Ser Ser Lys Ser Pro
850 855 860

aac cat ggg gtg aac ctt gtg gag aac ctg gac agc ctg ccc ccc aaa 2640
Asn His Gly Val Asn Leu Val Glu Asn Leu Asp Ser Leu Pro Pro Lys
865 870 875 880

gtt cca cag cgg gag gcc tcc ctg ggt ccc ccg gga gcc tcc ctg tct 2688
Val Pro Gln Arg Glu Ala Ser Leu Gly Pro Pro Gly Ala Ser Leu Ser
885 890 895

cag acc ggt cta agc aag cgg ctg gaa atg cac cac tcc tct tcc tac 2736
Gln Thr Gly Leu Ser Lys Arg Leu Glu Met His His Ser Ser Ser Tyr
900 905 910

ggg gtt gac tat aag agg agc tac ccc acg aac tcg ctc acg aga agc 2784
Gly Val Asp Tyr Lys Arg Ser Tyr Pro Thr Asn Ser Leu Thr Arg Ser
915 920 925

cac cag gcc acc act ctc aaa aga aac aac act aac tcc tcc aat tcc 2832
His Gln Ala Thr Thr Leu Lys Arg Asn Asn Thr Asn Ser Ser Asn Ser
930 935 940

tct cac ctc tcc aga aac cag agc ttt ggc agg gga gac aac ccg ccg 2880
Ser His Leu Ser Arg Asn Gln Ser Phe Gly Arg Gly Asp Asn Pro Pro
945 950 955 960

ccc gcc ccg cag agg gtg gac tcc atc cag gtg cac agc tcc cag cca 2928
Pro Ala Pro Gln Arg Val Asp Ser Ile Gln Val His Ser Ser Gln Pro
965 970 975

tct ggc cag gcc gtg act gtc tcg agg cag ccc agc ctc aac gcc tac 2976
Ser Gly Gln Ala Val Thr Val Ser Arg Gln Pro Ser Leu Asn Ala Tyr
980 985 990

aac tca ctg aca agg tcg ggg ctg aag cgt acg ccc tcg cta aag ccg 3024
Asn Ser Leu Thr Arg Ser Gly Leu Lys Arg Thr Pro Ser Leu Lys Pro
995 1000 1005

gac gta ccc ccc aaa cca tcc ttt gct ccc ctt tcc aca tcc atg aag 3072
Asp Val Pro Pro Lys Pro Ser Phe Ala Pro Leu Ser Thr Ser Met Lys
1010 1015 1020

ccc aat gat gcg tgt aca taa 3093
Pro Asn Asp Ala Cys Thr

1025 1030

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<213> Homo sapiens

<400> 2

Met	Arg	Ser	Glu	Ala	Leu	Leu	Leu	Tyr	Phe	Thr	Leu	Leu	His	Phe	Ala
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Gly	Ala	Gly	Phe	Pro	Glu	Asp	Ser	Glu	Pro	Ile	Ser	Ile	Ser	His	Gly
			20					25					30		
Asn	Tyr	Thr	Lys	Gln	Tyr	Pro	Val	Phe	Val	Gly	His	Lys	Pro	Gly	Arg
		35					40					45			
Asn	Thr	Thr	Gln	Arg	His	Arg	Leu	Asp	Ile	Gln	Met	Ile	Met	Ile	Met
	50					55					60				
Asn	Gly	Thr	Leu	Tyr	Ile	Ala	Ala	Arg	Asp	His	Ile	Tyr	Thr	Val	Asp
65					70					75					80
Ile	Asp	Thr	Ser	His	Thr	Glu	Glu	Ile	Tyr	Cys	Ser	Lys	Lys	Leu	Thr
				85					90					95	
Trp	Lys	Ser	Arg	Gln	Ala	Asp	Val	Asp	Thr	Cys	Arg	Met	Lys	Gly	Lys
			100					105					110		
His	Lys	Asp	Glu	Cys	His	Asn	Phe	Ile	Lys	Val	Leu	Leu	Lys	Lys	Asn
		115					120					125			
Asp	Asp	Ala	Leu	Phe	Val	Cys	Gly	Thr	Asn	Ala	Phe	Asn	Pro	Ser	Cys
	130					135					140				
Arg	Asn	Tyr	Lys	Met	Asp	Thr	Leu	Glu	Pro	Phe	Gly	Asp	Glu	Phe	Ser
145					150					155					160
Gly	Met	Ala	Arg	Cys	Pro	Tyr	Asp	Ala	Lys	His	Ala	Asn	Val	Ala	Leu
				165					170					175	
Phe	Ala	Asp	Gly	Lys	Leu	Tyr	Ser	Ala	Thr	Val	Thr	Asp	Phe	Leu	Ala
			180					185					190		
Ile	Asp	Ala	Val	Ile	Tyr	Arg	Ser	Leu	Gly	Glu	Ser	Pro	Thr	Leu	Arg
		195					200					205			

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Thr Val Lys His Asp Ser Lys Trp Leu Lys Glu Pro Tyr Phe Val Gln
    210                 215                 220

Ala Val Asp Tyr Gly Asp Tyr Ile Tyr Phe Phe Phe Arg Glu Ile Ala
225                 230                 235                 240

Val Glu Tyr Asn Thr Met Gly Lys Val Val Phe Pro Arg Val Ala Gln
                245                 250                 255

Val Cys Lys Asn Asp Met Gly Gly Ser Gln Arg Val Leu Glu Lys Gln
            260                 265                 270

Trp Thr Ser Phe Leu Lys Ala Arg Leu Asn Cys Ser Val Pro Gly Asp
        275                 280                 285

Ser His Phe Tyr Phe Asn Ile Leu Gln Ala Val Thr Asp Val Ile Arg
    290                 295                 300

Ile Asn Gly Arg Asp Val Val Leu Ala Thr Phe Ser Thr Pro Tyr Asn
305                 310                 315                 320

Ser Ile Pro Gly Ser Ala Val Cys Ala Tyr Asp Met Leu Asp Ile Ala
                325                 330                 335

Ser Val Phe Thr Gly Arg Phe Lys Glu Gln Lys Ser Pro Asp Ser Thr
            340                 345                 350

Trp Thr Pro Val Pro Asp Glu Arg Val Pro Lys Pro Arg Pro Gly Cys
        355                 360                 365

Cys Ala Gly Ser Ser Ser Leu Glu Arg Tyr Ala Thr Ser Asn Glu Phe
    370                 375                 380

Pro Asp Asp Thr Leu Asn Phe Ile Lys Thr His Pro Leu Met Asp Glu
385                 390                 395                 400

Ala Val Pro Ser Ile Phe Asn Arg Pro Trp Phe Leu Arg Thr Met Val
                405                 410                 415

Arg Tyr Arg Leu Thr Lys Ile Ala Val Asp Thr Ala Ala Gly Pro Tyr
            420                 425                 430

Gln Asn His Thr Val Val Phe Leu Gly Ser Glu Lys Gly Ile Ile Leu
        435                 440                 445

Lys Phe Leu Ala Arg Ile Gly Asn Ser Gly Phe Leu Asn Asp Ser Leu
    450                 455                 460
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Phe Leu Glu Glu Met Ser Val Tyr Asn Ser Glu Lys Cys Ser Tyr Asp
465                 470                 475                 480

Gly Val Glu Asp Lys Arg Ile Met Gly Met Gln Leu Asp Arg Ala Ser
                485                 490                 495

Ser Ser Leu Tyr Val Ala Phe Ser Thr Cys Val Ile Lys Val Pro Leu
            500                 505                 510

Gly Arg Cys Glu Arg His Gly Lys Cys Lys Lys Thr Cys Ile Ala Ser
        515                 520                 525

Arg Asp Pro Tyr Cys Gly Trp Ile Lys Glu Gly Gly Ala Cys Ser His
    530                 535                 540

Leu Ser Pro Asn Ser Arg Leu Thr Phe Glu Gln Asp Ile Glu Arg Gly
545                 550                 555                 560

Asn Thr Asp Gly Leu Gly Asp Cys His Asn Ser Phe Val Ala Leu Asn
                565                 570                 575

Gly His Ser Ser Ser Leu Leu Pro Ser Thr Thr Thr Ser Asp Ser Thr
            580                 585                 590

Ala Gln Glu Gly Tyr Glu Ser Arg Gly Gly Met Leu Asp Trp Lys His
        595                 600                 605

Leu Leu Asp Ser Pro Asp Ser Thr Asp Pro Leu Gly Ala Val Ser Ser
    610                 615                 620

His Asn His Gln Asp Lys Lys Gly Val Ile Arg Glu Ser Tyr Leu Lys
625                 630                 635                 640

Gly His Asp Gln Leu Val Pro Val Thr Leu Leu Ala Ile Ala Val Ile
                645                 650                 655

Leu Ala Phe Val Met Gly Ala Val Phe Ser Gly Ile Thr Val Tyr Cys
            660                 665                 670

Val Cys Asp His Arg Arg Lys Asp Val Ala Val Val Gln Arg Lys Glu
        675                 680                 685

Lys Glu Leu Thr His Ser Arg Arg Gly Ser Met Ser Ser Val Thr Lys
    690                 695                 700

Leu Ser Gly Leu Phe Gly Asp Thr Gln Ser Lys Asp Pro Lys Pro Glu
705                 710                 715                 720
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Ala Ile Leu Thr Pro Leu Met His Asn Gly Lys Leu Ala Thr Pro Gly
725 730 735

Asn Thr Ala Lys Met Leu Ile Lys Ala Asp Gln His His Leu Asp Leu
740 745 750

Thr Ala Leu Pro Thr Pro Glu Ser Thr Pro Thr Leu Gln Gln Lys Arg
755 760 765

Lys Pro Ser Arg Gly Ser Arg Glu Trp Glu Arg Asn Gln Asn Leu Ile
770 775 780

Asn Ala Cys Thr Lys Asp Met Pro Pro Met Gly Ser Pro Val Ile Pro
785 790 795 800

Thr Asp Leu Pro Leu Arg Ala Ser Pro Ser His Ile Pro Ser Val Val
805 810 815

Val Leu Pro Ile Thr Gln Gln Gly Tyr Gln His Glu Tyr Val Asp Gln
820 825 830

Pro Lys Met Ser Glu Val Ala Gln Met Ala Leu Glu Asp Gln Ala Ala
835 840 845

Thr Leu Glu Tyr Lys Thr Ile Lys Glu His Leu Ser Ser Lys Ser Pro
850 855 860

Asn His Gly Val Asn Leu Val Glu Asn Leu Asp Ser Leu Pro Pro Lys
865 870 875 880

Val Pro Gln Arg Glu Ala Ser Leu Gly Pro Pro Gly Ala Ser Leu Ser
885 890 895

Gln Thr Gly Leu Ser Lys Arg Leu Glu Met His His Ser Ser Ser Tyr
900 905 910

Gly Val Asp Tyr Lys Arg Ser Tyr Pro Thr Asn Ser Leu Thr Arg Ser
915 920 925

His Gln Ala Thr Thr Leu Lys Arg Asn Asn Thr Asn Ser Ser Asn Ser
930 935 940

Ser His Leu Ser Arg Asn Gln Ser Phe Gly Arg Gly Asp Asn Pro Pro
945 950 955 960

Pro Ala Pro Gln Arg Val Asp Ser Ile Gln Val His Ser Ser Gln Pro
965 970 975

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Ser Gly Gln Ala Val Thr Val Ser Arg Gln Pro Ser Leu Asn Ala Tyr
            980                 985                 990

Asn Ser Leu Thr Arg Ser Gly Leu Lys Arg Thr Pro Ser Leu Lys Pro
        995                1000                1005

Asp Val Pro Pro Lys Pro Ser Phe Ala Pro Leu Ser Thr Ser Met Lys
   1010                1015                1020

Pro Asn Asp Ala Cys Thr
025                1030
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Pro Pro Pro Ala Pro Gln Arg Val Asp Ser Ile Gln Val His Ser Ser
  1               5                  10                  15

cag cca tct ggc cag gcc gtg act gtc tcg agg cag ccc agc ctc aac   96
Gln Pro Ser Gly Gln Ala Val Thr Val Ser Arg Gln Pro Ser Leu Asn
             20                  25                  30

gcc tac aac tca ctg aca agg tcg ggg ctg aag cgt acg ccc tcg cta   144
Ala Tyr Asn Ser Leu Thr Arg Ser Gly Leu Lys Arg Thr Pro Ser Leu
         35                  40                  45

aag ccg gac gta ccc ccc aaa cca tcc ttt gct ccc ctt tcc aca tcc   192
Lys Pro Asp Val Pro Pro Lys Pro Ser Phe Ala Pro Leu Ser Thr Ser
     50                  55                  60

atg aag ccc aat gat gcg tgt aca                                  216
Met Lys Pro Asn Asp Ala Cys Thr
 65                  70
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<213> Homo sapiens

<400> 4

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Gln	Pro	Ser	Gly	Gln	Ala	Val	Thr	Val	Ser	Arg	Gln	Pro	Ser	Leu	Asn
			20					25					30		

Ala	Tyr	Asn	Ser	Leu	Thr	Arg	Ser	Gly	Leu	Lys	Arg	Thr	Pro	Ser	Leu
		35					40					45			

Lys	Pro	Asp	Val	Pro	Pro	Lys	Pro	Ser	Phe	Ala	Pro	Leu	Ser	Thr	Ser
	50					55					60				

Met	Lys	Pro	Asn	Asp	Ala	Cys	Thr
65				70			

<210> 5
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<213> Homo sapiens

<400> 5

Pro	Pro	Pro	Gln	Pro	Gln	Arg	Lys	Pro	Gln	Val	Gln	Leu	His	Val	Gln
1				5				10					15		

Pro	Gln	Ala	Lys	Pro	His	Val	Gln	Pro	Gln	Pro	Val	Ser	Ser	Ala	Asn
			20					25					30		

Thr	Gln	Pro	Arg	Gly	Pro	Leu	Ser	Gln	Ala	Pro	Thr	Pro	Ala	Pro	Lys
		35					40					45			

Phe	Ala	Pro	Val	Ala	Pro	Lys	Phe	Thr	Pro	Val	Val	Ser	Lys	Phe	Ser
	50					55					60				

Pro	
65	

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agcggccagc atcaccacac ccgcggcacc gcgctgccgg ccgcagagcc gggccagagc 180

cttgcccccc tcccccagcc cccaccccgc cccccgccct gaaatgactt gttaatcggc 240

gcagacacca ccaaggggac tcaccgaagt ggaatccaag tggaatttgg atttggagaa 300

gagtttcttg aacatttacc ctcttccttg ttggttttct ttttcttttt cttctttttt 360

tttttggctt ctttttttcct ctccccttct ccgctcgtca ttggagatga acacatcgcg 420

tttgcatccc agaaagtagt cgccgcgact atttccccca aagagacaag cacacatgta 480

ggaatgacaa aggcttgcga aggagagagc cgcagccgcg gcccggagag atcccctcga 540

taatggatta ctaaatggga tacacgctgt accagttcgc tccgagcccc ggccgcctgt 600

ccgtcgatgc accgaaaagg gtgaagtaga gaaataaagt ctccccgctg aactact 657

atg agg tca gaa gcc ttg ctg cta tat ttc aca ctg cta cac ttt gct 705
Met Arg Ser Glu Ala Leu Leu Leu Tyr Phe Thr Leu Leu His Phe Ala
1 5 10 15

ggg gct ggt ttc cca gaa gat tct gag cca atc agt att tcg cat ggc 753
Gly Ala Gly Phe Pro Glu Asp Ser Glu Pro Ile Ser Ile Ser His Gly
20 25 30

aac tat aca aaa cag tat ccg gtg ttt gtg ggc cac aag cca gga cgg 801
Asn Tyr Thr Lys Gln Tyr Pro Val Phe Val Gly His Lys Pro Gly Arg
35 40 45

aac acc aca cag agg cac agg ctg gac atc cag atg att atg atc atg 849
Asn Thr Thr Gln Arg His Arg Leu Asp Ile Gln Met Ile Met Ile Met
50 55 60

aac gga acc ctc tac att gct gct agg gac cat att tat act gtt gat 897
Asn Gly Thr Leu Tyr Ile Ala Ala Arg Asp His Ile Tyr Thr Val Asp
65 70 75 80

ata gac aca tca cac acg gaa gaa att tat tgt agc aaa aaa ctg aca 945

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Ile Asp Thr Ser His Thr Glu Glu Ile Tyr Cys Ser Lys Lys Leu Thr
                 85                  90                  95

tgg aaa tct aga cag gcc gat gta gac aca tgc aga atg aag gga aaa   993
Trp Lys Ser Arg Gln Ala Asp Val Asp Thr Cys Arg Met Lys Gly Lys
            100                 105                 110

cat aag gat gag tgc cac aac ttt att aaa gtt ctt cta aag aaa aac   1041
His Lys Asp Glu Cys His Asn Phe Ile Lys Val Leu Leu Lys Lys Asn
        115                 120                 125

gat gat gca ttg ttt gtc tgt gga act aat gcc ttc aac cct tcc tgc   1089
Asp Asp Ala Leu Phe Val Cys Gly Thr Asn Ala Phe Asn Pro Ser Cys
    130                 135                 140

aga aac tat aag atg gat aca ttg gaa cca ttc ggg gat gaa ttc agc   1137
Arg Asn Tyr Lys Met Asp Thr Leu Glu Pro Phe Gly Asp Glu Phe Ser
145                 150                 155                 160

gga atg gcc aga tgc cca tat gat gcc aaa cat gcc aac gtt gca ctg   1185
Gly Met Ala Arg Cys Pro Tyr Asp Ala Lys His Ala Asn Val Ala Leu
                165                 170                 175

ttt gca gat gga aaa cta tac tca gcc aca gtg act gac ttc ctt gcc   1233
Phe Ala Asp Gly Lys Leu Tyr Ser Ala Thr Val Thr Asp Phe Leu Ala
            180                 185                 190

att gac gca gtc att tac cgg agt ctt gga gaa agc cct acc ctg cgg   1281
Ile Asp Ala Val Ile Tyr Arg Ser Leu Gly Glu Ser Pro Thr Leu Arg
        195                 200                 205

acc gtc aag cac gat tca aaa tgg ttg aaa gaa cca tac ttt gtt caa   1329
Thr Val Lys His Asp Ser Lys Trp Leu Lys Glu Pro Tyr Phe Val Gln
    210                 215                 220

gcc gtg gat tac gga gat tat atc tac ttc ttc ttc agg gaa ata gca   1377
Ala Val Asp Tyr Gly Asp Tyr Ile Tyr Phe Phe Phe Arg Glu Ile Ala
225                 230                 235                 240

gtg gag tat aac acc atg gga aag gta gtt ttc cca aga gtg gct cag   1425
Val Glu Tyr Asn Thr Met Gly Lys Val Val Phe Pro Arg Val Ala Gln
                245                 250                 255

gtt tgt aag aat gat atg gga gga tct caa aga gtc ctg gag aaa cag   1473
Val Cys Lys Asn Asp Met Gly Gly Ser Gln Arg Val Leu Glu Lys Gln
            260                 265                 270

tgg acg tcg ttc ctg aag gcg cgc ttg aac tgc tca gtt cct gga gac   1521
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Trp Thr Ser Phe Leu Lys Ala Arg Leu Asn Cys Ser Val Pro Gly Asp
275 280 285

tct cat ttt tat ttc aac att ctc cag gca gtt aca gat gtg att cgt 1569
Ser His Phe Tyr Phe Asn Ile Leu Gln Ala Val Thr Asp Val Ile Arg
290 295 300

atc aac ggg cgt gat gtt gtc ctg gca acg ttt tct aca cct tat aac 1617
Ile Asn Gly Arg Asp Val Val Leu Ala Thr Phe Ser Thr Pro Tyr Asn
305 310 315 320

agc atc cct ggg tct gca gtc tgt gcc tat gac atg ctt gac att gcc 1665
Ser Ile Pro Gly Ser Ala Val Cys Ala Tyr Asp Met Leu Asp Ile Ala
325 330 335

agt gtt ttt act ggg aga ttc aag gaa cag aag tct cct gat tcc acc 1713
Ser Val Phe Thr Gly Arg Phe Lys Glu Gln Lys Ser Pro Asp Ser Thr
340 345 350

tgg aca cca gtt cct gat gaa cga gtt cct aag ccc agg cca ggt tgc 1761
Trp Thr Pro Val Pro Asp Glu Arg Val Pro Lys Pro Arg Pro Gly Cys
355 360 365

tgt gct ggc tca tcc tcc tta gaa aga tat gca acc tcc aat gag ttc 1809
Cys Ala Gly Ser Ser Ser Leu Glu Arg Tyr Ala Thr Ser Asn Glu Phe
370 375 380

cct gat gat acc ctg aac ttc atc aag acg cac ccg ctc atg gat gag 1857
Pro Asp Asp Thr Leu Asn Phe Ile Lys Thr His Pro Leu Met Asp Glu
385 390 395 400

gca gtg ccc tcc atc ttc aac agg cca tgg ttc ctg aga aca atg gtc 1905
Ala Val Pro Ser Ile Phe Asn Arg Pro Trp Phe Leu Arg Thr Met Val
405 410 415

aga tac cgc ctt acc aaa att gca gtg gac aca gct gct ggg cca tat 1953
Arg Tyr Arg Leu Thr Lys Ile Ala Val Asp Thr Ala Ala Gly Pro Tyr
420 425 430

cag aat cac act gtg gtt ttt ctg gga tca gag aag gga atc atc ttg 2001
Gln Asn His Thr Val Val Phe Leu Gly Ser Glu Lys Gly Ile Ile Leu
435 440 445

aag ttt ttg gcc aga ata gga aat agt ggt ttt cta aat gac agc ctt 2049
Lys Phe Leu Ala Arg Ile Gly Asn Ser Gly Phe Leu Asn Asp Ser Leu
450 455 460

ttc ctg gag gag atg agt gtt tac aac tct gaa aaa tgc agc tat gat 2097

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Phe Leu Glu Glu Met Ser Val Tyr Asn Ser Glu Lys Cys Ser Tyr Asp
465                 470                 475                 480

gga gtc gaa gac aaa agg atc atg ggc atg cag ctg gac aga gca agc   2145
Gly Val Glu Asp Lys Arg Ile Met Gly Met Gln Leu Asp Arg Ala Ser
                485                 490                 495

agc tct ctg tat gtt gcg ttc tct acc tgt gtg ata aag gtt ccc ctt   2193
Ser Ser Leu Tyr Val Ala Phe Ser Thr Cys Val Ile Lys Val Pro Leu
            500                 505                 510

ggc cgg tgt gaa cga cat ggg aag tgt aaa aaa acc tgt att gcc tcc   2241
Gly Arg Cys Glu Arg His Gly Lys Cys Lys Lys Thr Cys Ile Ala Ser
        515                 520                 525

aga gac cca tat tgt gga tgg ata aag gaa ggt ggt gcc tgc agc cat   2289
Arg Asp Pro Tyr Cys Gly Trp Ile Lys Glu Gly Gly Ala Cys Ser His
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tta tca ccc aac agc aga ctg act ttt gag cag gac ata gag cgt ggc   2337
Leu Ser Pro Asn Ser Arg Leu Thr Phe Glu Gln Asp Ile Glu Arg Gly
545                 550                 555                 560

aat aca gat ggt ctg ggg gac tgt cac aat tcc ttt gtg gca ctg aat   2385
Asn Thr Asp Gly Leu Gly Asp Cys His Asn Ser Phe Val Ala Leu Asn
                565                 570                 575

ggg cat tcc agt tcc ctc ttg ccc agc aca acc aca tca gat tcg acg   2433
Gly His Ser Ser Ser Leu Leu Pro Ser Thr Thr Thr Ser Asp Ser Thr
            580                 585                 590

gct caa gag ggg tat gag tct agg gga gga atg ctg gac tgg aag cat   2481
Ala Gln Glu Gly Tyr Glu Ser Arg Gly Gly Met Leu Asp Trp Lys His
        595                 600                 605

ctg ctt gac tca cct gac agc aca gac cct ttg ggg gca gtg tct tcc   2529
Leu Leu Asp Ser Pro Asp Ser Thr Asp Pro Leu Gly Ala Val Ser Ser
    610                 615                 620

cat aat cac caa gac aag aag gga gtg att cgg gaa agt tac ctc aaa   2577
His Asn His Gln Asp Lys Lys Gly Val Ile Arg Glu Ser Tyr Leu Lys
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ggc cac gac cag ctg gtt ccc gtc acc ctc ttg gcc att gca gtc atc   2625
Gly His Asp Gln Leu Val Pro Val Thr Leu Leu Ala Ile Ala Val Ile
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Val Cys Asp His Arg Arg Lys Asp Val Ala Val Val Gln Arg Lys Glu
        675                 680                 685

aag gag ctc acc cac tcg cgc cgg ggc tcc atg agc agc gtc acc aag   2769
Lys Glu Leu Thr His Ser Arg Arg Gly Ser Met Ser Ser Val Thr Lys
    690                 695                 700

ctc agc ggc ctc ttt ggg gac act caa tcc aaa gac cca aag ccg gag   2817
Leu Ser Gly Leu Phe Gly Asp Thr Gln Ser Lys Asp Pro Lys Pro Glu
705                 710                 715                 720

gcc atc ctc acg cca ctc atg cac aac ggc aag ctc gcc act ccc ggc   2865
Ala Ile Leu Thr Pro Leu Met His Asn Gly Lys Leu Ala Thr Pro Gly
                725                 730                 735

aac acg gcc aag atg ctc att aaa gca gac cag cac cac ctg gac ctg   2913
Asn Thr Ala Lys Met Leu Ile Lys Ala Asp Gln His His Leu Asp Leu
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acg gcc ctc ccc acc cca gag tca acc cca acg ctg cag cag aag cgg   2961
Thr Ala Leu Pro Thr Pro Glu Ser Thr Pro Thr Leu Gln Gln Lys Arg
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aag ccc agc cgc ggc agc cgc gag tgg gag agg aac cag aac ctc atc   3009
Lys Pro Ser Arg Gly Ser Arg Glu Trp Glu Arg Asn Gln Asn Leu Ile
    770                 775                 780

aat gcc tgc aca aag gac atg ccc ccc atg ggc tcc cct gtg att ccc   3057
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785                 790                 795                 800

acg gac ctg ccc ctg cgg gcc tcc ccc agc cac atc ccc agc gtg gtg   3105
Thr Asp Leu Pro Leu Arg Ala Ser Pro Ser His Ile Pro Ser Val Val
                805                 810                 815

gtc ctg ccc atc acg cag cag ggc tac cag cat gag tac gtg gac cag   3153
Val Leu Pro Ile Thr Gln Gln Gly Tyr Gln His Glu Tyr Val Asp Gln
            820                 825                 830

ccc aaa atg agc gag gtg gcc cag atg gcg ctg gag gac cag gcc gcc   3201
Pro Lys Met Ser Glu Val Ala Gln Met Ala Leu Glu Asp Gln Ala Ala
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aca ctg gag tat aag acc atc aag gaa cat ctc agc agc aag agt ccc   3249
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Asn His Gly Val Asn Leu Val Glu Asn Leu Asp Ser Leu Pro Pro Lys
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Val Pro Gln Arg Glu Ala Ser Leu Gly Pro Pro Gly Ala Ser Leu Ser
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cag acc ggt cta agc aag cgg ctg gaa atg cac cac tcc tct tcc tac   3393
Gln Thr Gly Leu Ser Lys Arg Leu Glu Met His His Ser Ser Ser Tyr
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ggg gtt gac tat aag agg agc tac ccc acg aac tcg ctc acg aga agc   3441
Gly Val Asp Tyr Lys Arg Ser Tyr Pro Thr Asn Ser Leu Thr Arg Ser
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cac cag gcc acc act ctc aaa aga aac aac act aac tcc tcc aat tcc   3489
His Gln Ala Thr Thr Leu Lys Arg Asn Asn Thr Asn Ser Ser Asn Ser
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tct cac ctc tcc aga aac cag agc ttt ggc agg gga gac aac ccg ccg   3537
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ccc gcc ccg cag agg gtg gac tcc atc cag gtg cac agc tcc cag cca   3585
Pro Ala Pro Gln Arg Val Asp Ser Ile Gln Val His Ser Ser Gln Pro
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tct ggc cag gcc gtg act gtc tcg agg cag ccc agc ctc aac gcc tac   3633
Ser Gly Gln Ala Val Thr Val Ser Arg Gln Pro Ser Leu Asn Ala Tyr
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aac tca ctg aca agg tcg ggg ctg aag cgt acg ccc tcg cta aag ccg   3681
Asn Ser Leu Thr Arg Ser Gly Leu Lys Arg Thr Pro Ser Leu Lys Pro
        995                1000                1005

gac gta ccc ccc aaa cca tcc ttt gct ccc ctt tcc aca tcc atg aag   3729
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<400> 7

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Asn Thr Thr Gln Arg His Arg Leu Asp Ile Gln Met Ile Met Ile Met
50 55 60

Asn Gly Thr Leu Tyr Ile Ala Ala Arg Asp His Ile Tyr Thr Val Asp
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Ile Asp Thr Ser His Thr Glu Glu Ile Tyr Cys Ser Lys Lys Leu Thr
85 90 95

Trp Lys Ser Arg Gln Ala Asp Val Asp Thr Cys Arg Met Lys Gly Lys
100 105 110

His Lys Asp Glu Cys His Asn Phe Ile Lys Val Leu Leu Lys Lys Asn
115 120 125

Asp Asp Ala Leu Phe Val Cys Gly Thr Asn Ala Phe Asn Pro Ser Cys
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Arg Asn Tyr Lys Met Asp Thr Leu Glu Pro Phe Gly Asp Glu Phe Ser
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Gly Met Ala Arg Cys Pro Tyr Asp Ala Lys His Ala Asn Val Ala Leu
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Phe Ala Asp Gly Lys Leu Tyr Ser Ala Thr Val Thr Asp Phe Leu Ala
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Ile Asp Ala Val Ile Tyr Arg Ser Leu Gly Glu Ser Pro Thr Leu Arg
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Thr Val Lys His Asp Ser Lys Trp Leu Lys Glu Pro Tyr Phe Val Gln
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Ala Val Asp Tyr Gly Asp Tyr Ile Tyr Phe Phe Phe Arg Glu Ile Ala
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Val Glu Tyr Asn Thr Met Gly Lys Val Val Phe Pro Arg Val Ala Gln
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Val Cys Lys Asn Asp Met Gly Gly Ser Gln Arg Val Leu Glu Lys Gln
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Trp Thr Ser Phe Leu Lys Ala Arg Leu Asn Cys Ser Val Pro Gly Asp
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Ser His Phe Tyr Phe Asn Ile Leu Gln Ala Val Thr Asp Val Ile Arg
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Ile Asn Gly Arg Asp Val Val Leu Ala Thr Phe Ser Thr Pro Tyr Asn
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Ser Ile Pro Gly Ser Ala Val Cys Ala Tyr Asp Met Leu Asp Ile Ala
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Cys Ala Gly Ser Ser Ser Leu Glu Arg Tyr Ala Thr Ser Asn Glu Phe
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Ala Val Pro Ser Ile Phe Asn Arg Pro Trp Phe Leu Arg Thr Met Val
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Arg Tyr Arg Leu Thr Lys Ile Ala Val Asp Thr Ala Ala Gly Pro Tyr
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Gln Asn His Thr Val Val Phe Leu Gly Ser Glu Lys Gly Ile Ile Leu
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Lys Phe Leu Ala Arg Ile Gly Asn Ser Gly Phe Leu Asn Asp Ser Leu
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Phe Leu Glu Glu Met Ser Val Tyr Asn Ser Glu Lys Cys Ser Tyr Asp
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Gly Val Glu Asp Lys Arg Ile Met Gly Met Gln Leu Asp Arg Ala Ser
                485                 490                 495

Ser Ser Leu Tyr Val Ala Phe Ser Thr Cys Val Ile Lys Val Pro Leu
            500                 505                 510

Gly Arg Cys Glu Arg His Gly Lys Cys Lys Lys Thr Cys Ile Ala Ser
        515                 520                 525

Arg Asp Pro Tyr Cys Gly Trp Ile Lys Glu Gly Gly Ala Cys Ser His
    530                 535                 540

Leu Ser Pro Asn Ser Arg Leu Thr Phe Glu Gln Asp Ile Glu Arg Gly
545                 550                 555                 560

Asn Thr Asp Gly Leu Gly Asp Cys His Asn Ser Phe Val Ala Leu Asn
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Gly His Ser Ser Ser Leu Leu Pro Ser Thr Thr Thr Ser Asp Ser Thr
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Ala Gln Glu Gly Tyr Glu Ser Arg Gly Gly Met Leu Asp Trp Lys His
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Leu Leu Asp Ser Pro Asp Ser Thr Asp Pro Leu Gly Ala Val Ser Ser
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His Asn His Gln Asp Lys Lys Gly Val Ile Arg Glu Ser Tyr Leu Lys
625                 630                 635                 640

Gly His Asp Gln Leu Val Pro Val Thr Leu Leu Ala Ile Ala Val Ile
                645                 650                 655

Leu Ala Phe Val Met Gly Ala Val Phe Ser Gly Ile Thr Val Tyr Cys
            660                 665                 670

Val Cys Asp His Arg Arg Lys Asp Val Ala Val Val Gln Arg Lys Glu
        675                 680                 685

Lys Glu Leu Thr His Ser Arg Arg Gly Ser Met Ser Ser Val Thr Lys
    690                 695                 700

Leu Ser Gly Leu Phe Gly Asp Thr Gln Ser Lys Asp Pro Lys Pro Glu
705                 710                 715                 720
```

Ala Ile Leu Thr Pro Leu Met His Asn Gly Lys Leu Ala Thr Pro Gly
725 730 735

Asn Thr Ala Lys Met Leu Ile Lys Ala Asp Gln His His Leu Asp Leu
740 745 750

Thr Ala Leu Pro Thr Pro Glu Ser Thr Pro Thr Leu Gln Gln Lys Arg
755 760 765

Lys Pro Ser Arg Gly Ser Arg Glu Trp Glu Arg Asn Gln Asn Leu Ile
770 775 780

Asn Ala Cys Thr Lys Asp Met Pro Pro Met Gly Ser Pro Val Ile Pro
785 790 795 800

Thr Asp Leu Pro Leu Arg Ala Ser Pro Ser His Ile Pro Ser Val Val
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Val Leu Pro Ile Thr Gln Gln Gly Tyr Gln His Glu Tyr Val Asp Gln
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Pro Lys Met Ser Glu Val Ala Gln Met Ala Leu Glu Asp Gln Ala Ala
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Thr Leu Glu Tyr Lys Thr Ile Lys Glu His Leu Ser Ser Lys Ser Pro
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Asn His Gly Val Asn Leu Val Glu Asn Leu Asp Ser Leu Pro Pro Lys
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Val Pro Gln Arg Glu Ala Ser Leu Gly Pro Pro Gly Ala Ser Leu Ser
885 890 895

Gln Thr Gly Leu Ser Lys Arg Leu Glu Met His His Ser Ser Ser Tyr
900 905 910

Gly Val Asp Tyr Lys Arg Ser Tyr Pro Thr Asn Ser Leu Thr Arg Ser
915 920 925

His Gln Ala Thr Thr Leu Lys Arg Asn Asn Thr Asn Ser Ser Asn Ser
930 935 940

Ser His Leu Ser Arg Asn Gln Ser Phe Gly Arg Gly Asp Asn Pro Pro
945 950 955 960

Pro Ala Pro Gln Arg Val Asp Ser Ile Gln Val His Ser Ser Gln Pro
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Ser Gly Gln Ala Val Thr Val Ser Arg Gln Pro Ser Leu Asn Ala Tyr
980 985 990

Asn Ser Leu Thr Arg Ser Gly Leu Lys Arg Thr Pro Ser Leu Lys Pro
995 1000 1005

Asp Val Pro Pro Lys Pro Ser Phe Ala Pro Leu Ser Thr Ser Met Lys
1010 1015 1020

Pro Asn Asp Ala Cys Thr
025 1030

Claims

1. Nucleic acid coding for human semaphorin 6A-1 comprising:
   (a) the nucleotide sequence shown in SEQ ID NO:1,
   (b) a sequence corresponding to the nucleotide sequence shown in SEQ ID NO:1 within the degeneration of the genetic code, or
   (c) a sequence which hybridizes with the sequences of (a) or/and (b) under stringent conditions.

2. Nucleic acid coding for a binding domain of human semaphorin 6A-1 comprising:
   (a) the nucleotide sequence shown in SEQ ID NO:3,
   (b) a sequence corresponding to the nucleotide sequence shown in SEQ ID NO:3 within the degeneration of the genetic code, or
   (c) a sequence which hybridizes with the sequences of (a) or/and (b) under stringent conditions.

3. Nucleic acid according to claim 1 or 2,
characterized in that it has a homology greater than 80% to the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:3.

4. Modified nucleic acid or nucleic acid analog having a nucleotide sequence according to claims 1-3, or a section having at least 12 bases therefrom.

5. A nucleic acid which encodes a protein having a semaphorin domain and which hybridizes under stringent conditions to a nucleic acid comprising the nucleotide sequence shown in SEQ ID NO:1.

6. Nucleic acid according to any of the preceding claims, which encodes a protein inhibiting neurite outgrowth.

7. Nucleic acid according to claim 6, which encodes a protein inhibiting neurite outgrowth of CNS-neuron.

8. Recombinant vector,
characterized in that it contains at least one copy of a nucleic acid according to claims 1-7, or a section therefrom.

9. Vector according to claim 8,
characterized in that it is a eukaryotic vector.

10. Cell,
characterized in that it is transformed with a nucleic acid according to any of claims 1-7 or with a vector according to claim 8 or 9.

11. Polypeptide encoded by a nucleic acid according to claims 1-7.

12. Polypeptide according to claim 11 being a fusion protein comprising a polypeptide encoded by a nucleic acid according to claims 1-7 and at least one further polypeptide.

13. Use of the polypeptide according to claim 11 or 12 or of fragments of said polypeptide as immunogen for the production of antibodies.

14. Antibodies against a polypeptide according to claim 11 or 12.

15. Pharmaceutical composition comprising:
(a) a nucleic acid according to any of claims 1-7,
(b) a recombinant vector according to claim 8 or 9,
(c) a cell according to claim 10,

(d) a polypeptide according to claim 11 or 12, or/and

(e) an antibody according to claim 14.

16. Use of a peptide according to claim 11 or 12 for the preparation of a pharmaceutical composition.

17. Use of a composition according to claim 15 as diagnostic agent.

18. Use of a composition according to claim 15 for the production of a therapeutic agent.

19. Use according to claim 18 for the modulation of the immune system.

20. Use according to any of claims 17-19 in gene therapy.

21. Use according to any of claims 17-20 for effecting differentiation, cytoskeletal stabilization and/or plasticity.

1/11

Fig. 1

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Fig. 1 (cont.)

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Fig. 2

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TTGAACTGCTCAGTTCCTGGAGACTCTCATTTTTATTTCAACATTCTCCAGGCAGTTACA  1537
 L  N  C  S  V  P  G  D  S  H  F  Y  F  N  I  L  Q  A  V  T
GATGTGATTCGTATCAACGGGCGTGATGTTGTCCTGGCAACGTTTTCTACACCTTATAAC  1597
 D  V  I  R  I  N  G  R  D  V  V  L  A  T  F  S  T  P  Y  N
AGCATCCCTGGGTCTGCAGTCTGTGCCTATGACATGCTTGACATTGCCAGTGTTTTTACT  1657
 S  I  P  G  S  A  V  C  A  Y  D  M  L  D  I  A  S  V  F  T
```

Fig. 2 (cont.)

```
GGGAGATTCAAGGAACAGAAGTCTCCTGATTCCACCTGGACACCAGTTCCTGATGAACGA  1717
 G  R  F  K  E  Q  K  S  P  D  S  T  W  T  P  V  P  D  E  R
GTTCCTAAGCCCAGGCCAGGTTGCTGTGCTGGCTCATCCTCCTTAGAAAGATATGCAACC  1777
 V  P  K  P  R  P  G  C  C  A  G  S  S  S  L  E  R  Y  A  T
TCCAATGAGTTCCCTGATGATACCCTGAACTTCATCAAGACGCACCCGCTCATGGATGAG  1837
 S  N  E  F  P  D  D  T  L  N  F  I  K  T  H  P  L  M  D  E
GCAGTGCCCTCCATCTTCAACAGGCCATGGTTCCTGAGAACAATGGTCAGATACCGCCTT  1897
 A  V  P  S  I  F  N  R  P  W  F  L  R  T  M  V  R  Y  R  L
ACCAAAATTGCAGTGGACACAGCTGCTGGGCCATATCAGAATCACACTGTGGTTTTTCTG  1957
 T  K  I  A  V  D  T  A  A  G  P  Y  Q  N  H  T  V  V  F  L
GGATCAGAGAAGGGAATCATCTTGAAGTTTTTGGCCAGAATAGGAAATAGTGGTTTTCTA  2017
 G  S  E  K  G  I  I  L  K  F  L  A  R  I  G  N  S  G  F  L
AATGACAGCCTTTTCCTGGAGGAGATGAGTGTTTACAACTCTGAAAAATGCAGCTATGAT  2077
 N  D  S  L  F  L  E  E  M  S  V  Y  N  S  E  K  C  S  Y  D
GGAGTCGAAGACAAAAGGATCATGGGCATGCAGCTGGACAGAGCAAGCAGCTCTCTGTAT  2137
 G  V  E  D  K  R  I  M  G  M  Q  L  D  R  A  S  S  S  L  Y
GTTGCGTTCTCTACCTGTGTGATAAAGGTTCCCCTTGGCCGGTGTGAACGACATGGGAAG  2197
 V  A  F  S  T  C  V  I  K  V  P  L  G  R  C  E  R  H  G  K
TGTAAAAAAACCTGTATTGCCTCCAGAGACCCATATTGTGGATGGATAAAGGAAGGTGGT  2257
 C  K  K  T  C  I  A  S  R  D  P  Y  C  G  W  I  K  E  G  G
GCCTGCAGCCATTTATCACCCAACAGCAGACTGACTTTTGAGCAGGACATAGAGCGTGGC  2317
 A  C  S  H  L  S  P  N  S  R  L  T  F  E  Q  D  I  E  R  G
AATACAGATGGTCTGGGGGACTGTCACAATTCCTTTGTGGCACTGAATGGGCATTCCAGT  2377
 N  T  D  G  L  G  D  C  H  N  S  F  V  A  L  N  G  H  S  S
TCCCTCTTGCCCAGCACAACCACATCAGATTCGACGGCTCAAGAGGGGTATGAGTCTAGG  2437
 S  L  L  P  S  T  T  T  S  D  S  T  A  Q  E  G  Y  E  S  R
GGAGGAATGCTGGACTGGAAGCATCTGCTTGACTCACCTGACAGCACAGACCCTTTGGGG  2497
 G  G  M  L  D  W  K  H  L  L  D  S  P  D  S  T  D  P  L  G
GCAGTGTCTTCCCATAATCACCAAGACAAGAAGGGAGTGATTCGGGAAAGTTACCTCAAA  2557
 A  V  S  S  H  N  H  Q  D  K  K  G  V  I  R  E  S  Y  L  K
GGCCACGACCAGCTGGTTCCCGTCACCCTCTTGGCCATTGCAGTCATCCTGGCTTTCGTC  2617
 G  H  D  Q  L  V  P  V  T  L  L  A  I  A  V  I  L  A  F  V
ATGGGGGCCGTCTTCTCGGGCATCACCGTCTACTGCGTCTGTGATCATCGGCGCAAAGAC  2677
 M  G  A  V  F  S  G  I  T  V  Y  C  V  C  D  H  R  R  K  D
GTGGCTGTGGTGCAGCGCAAGGAGAAGGAGCTCACCCACTCGCGCCGGGGCTCCATGAGC  2737
 V  A  V  V  Q  R  K  E  K  E  L  T  H  S  R  R  G  S  M  S
AGCGTCACCAAGCTCAGCGGCCTCTTTGGGGACACTCAATCCAAAGACCCAAAGCCGGAG  2797
 S  V  T  K  L  S  G  L  F  G  D  T  Q  S  K  D  P  K  P  E
GCCATCCTCACGCCACTCATGCACAACGGCAAGCTCGCCACTCCCGGCAACACGGCCAAG  2857
 A  I  L  T  P  L  M  H  N  G  K  L  A  T  P  G  N  T  A  K
ATGCTCATTAAAGCAGACCAGCACCACCTGGACCTGACGGCCCTCCCCACCCCAGAGTCA  2917
 M  L  I  K  A  D  Q  H  H  L  D  L  T  A  L  P  T  P  E  S
ACCCCAACGCTGCAGCAGAAGCGGAAGCCCAGCCGCGGCAGCCGCGAGTGGGAGAGGAAC  2977
 T  P  T  L  Q  Q  K  R  K  P  S  R  G  S  R  E  W  E  R  N
CAGAACCTCATCAATGCCTGCACAAAGGACATGCCCCCCATGGGCTCCCCTGTGATTCCC  3037
 Q  N  L  I  N  A  C  T  K  D  M  P  P  M  G  S  P  V  I  P
```

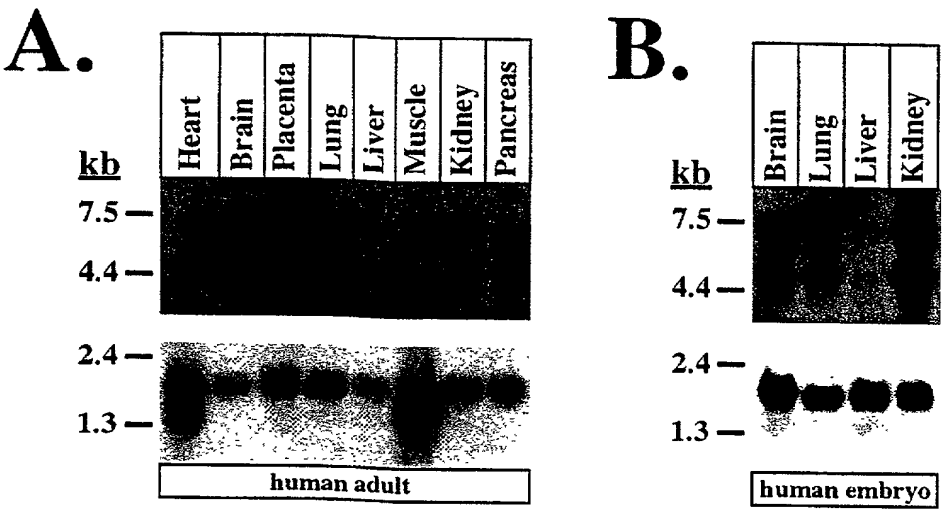
Fig. 2 (cont.)

```
ACGGACCTGCCCCTGCGGGCCTCCCCCAGCCACATCCCCAGCGTGGTGGTCCTGCCCATC  3097
 T  D  L  P  L  R  A  S  P  S  H  I  P  S  V  V  V  L  P  I
ACGCAGCAGGGCTACCAGCATGAGTACGTGGACCAGCCCAAAATGAGCGAGGTGGCCCAG  3157
 T  Q  Q  G  Y  Q  H  E  Y  V  D  Q  P  K  M  S  E  V  A  Q
ATGGCGCTGGAGGACCAGGCCGCCACACTGGAGTATAAGACCATCAAGGAACATCTCAGC  3217
 M  A  L  E  D  Q  A  A  T  L  E  Y  K  T  I  K  E  H  L  S
AGCAAGAGTCCCAACCATGGGGTGAACCTTGTGGAGAACCTGGACAGCCTGCCCCCCAAA  3277
 S  K  S  P  N  H  G  V  N  L  V  E  N  L  D  S  L  P  P  K
GTTCCACAGCGGGAGGCCTCCCTGGGTCCCCCGGGAGCCTCCCTGTCTCAGACCGGTCTA  3337
 V  P  Q  R  E  A  S  L  G  P  P  G  A  S  L  S  Q  T  G  L
AGCAAGCGGCTGGAAATGCACCACTCCTCTTCCTACGGGGTTGACTATAAGAGGAGCTAC  3397
 S  K  R  L  E  M  H  H  S  S  S  Y  G  V  D  Y  K  R  S  Y
CCCACGAACTCGCTCACGAGAAGCCACCAGGCCACCACTCTCAAAAGAAACAACACTAAC  3457
 P  T  N  S  L  T  R  S  H  Q  A  T  T  L  K  R  N  N  T  N
TCCTCCAATTCCTCTCACCTCTCCAGAAACCAGAGCTTTGGCAGGGGAGACAACCCGCCG  3517
 S  S  N  S  S  H  L  S  R  N  Q  S  F  G  R  G  D  N  P  P
CCCGCCCCGCAGAGGGTGGACTCCATCCAGGTGCACAGCTCCCAGCCATCTGGCCAGGCC  3577
 P  A  P  Q  R  V  D  S  I  Q  V  H  S  S  Q  P  S  G  Q  A
GTGACTGTCTCGAGGCAGCCCAGCCTCAACGCCTACAACTCACTGACAAGGTCGGGGCTG  3637
 V  T  V  S  R  Q  P  S  L  N  A  Y  N  S  L  T  R  S  G  L
AAGCGTACGCCCTCGCTAAAGCCGGACGTACCCCCCAAACCATCCTTTGCTCCCCTTTCC  3697
 K  R  T  P  S  L  K  P  D  V  P  P  K  P  S  F  A  P  L  S
ACATCCATGAAGCCCAATGATGCGTGTACATAAtcccaggggggaggggtcaggtgtcga  3757
 T  S  M  K  P  N  D  A  C  T  *

accagcaggcaaggcgaggtgcccgctcagctcagcaaggttctcaactgcctcgagtac  3817
ccaccagaccaagaaggcctgcggc
```

6/11

Fig. 3



(MMU)Sema6A-1 Distribution in Mouse Adult and Embryonic Tissues

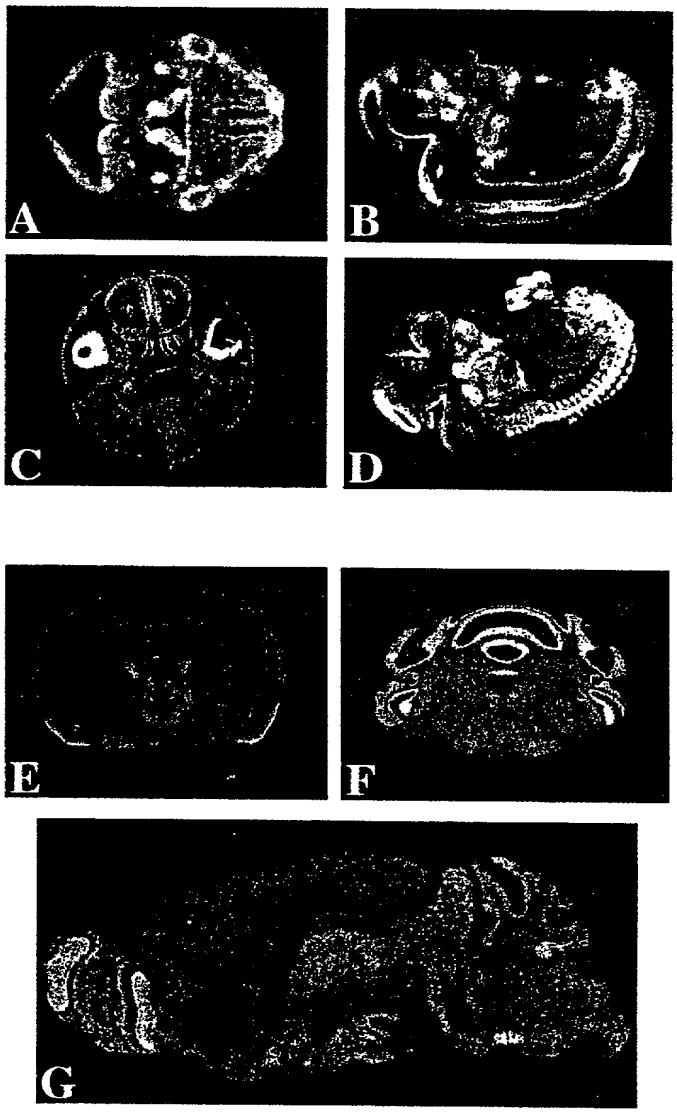


Fig. 4

(HSA)SEMA6A-1: Expression, Protein-Size and Dimerization

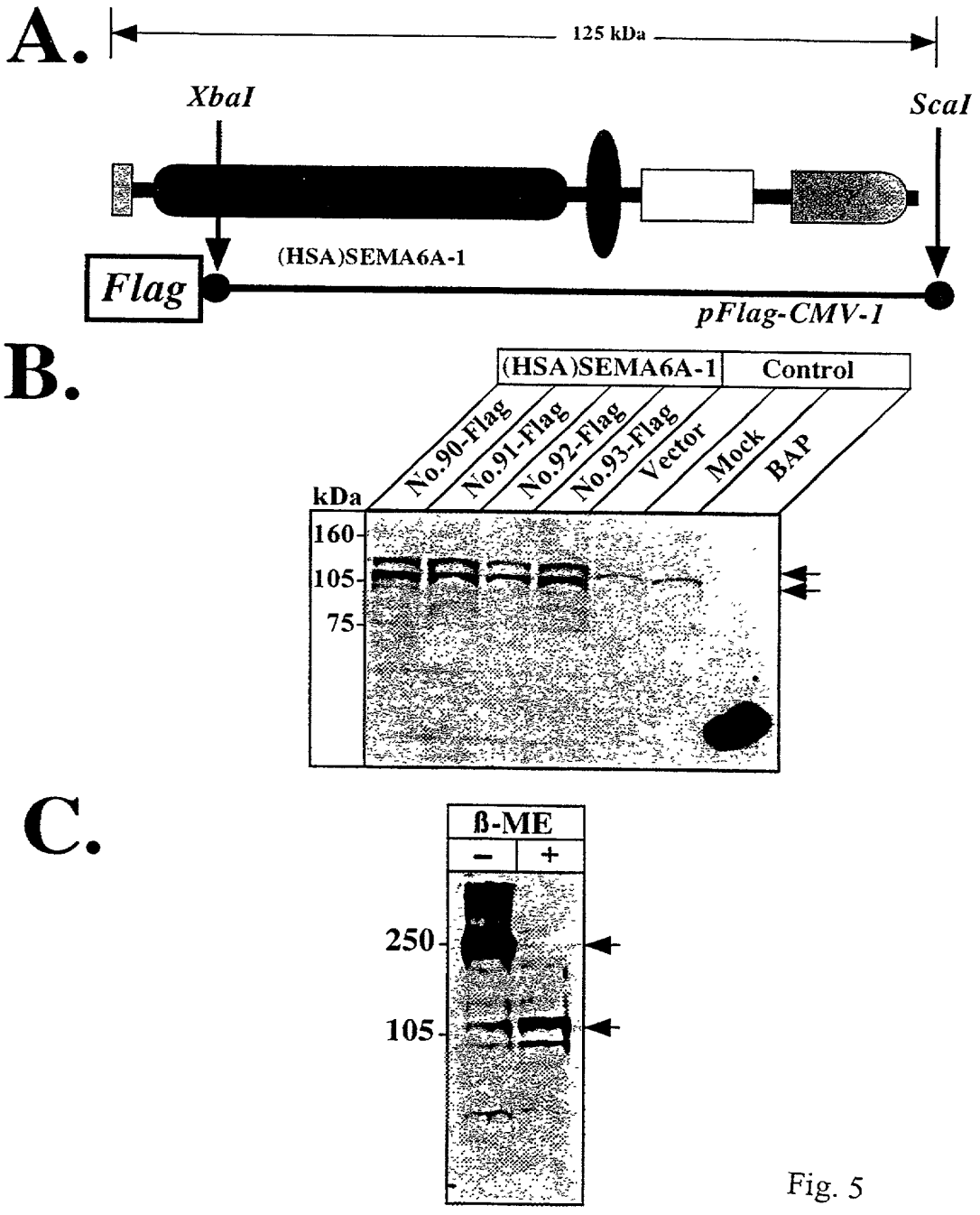


Fig. 5

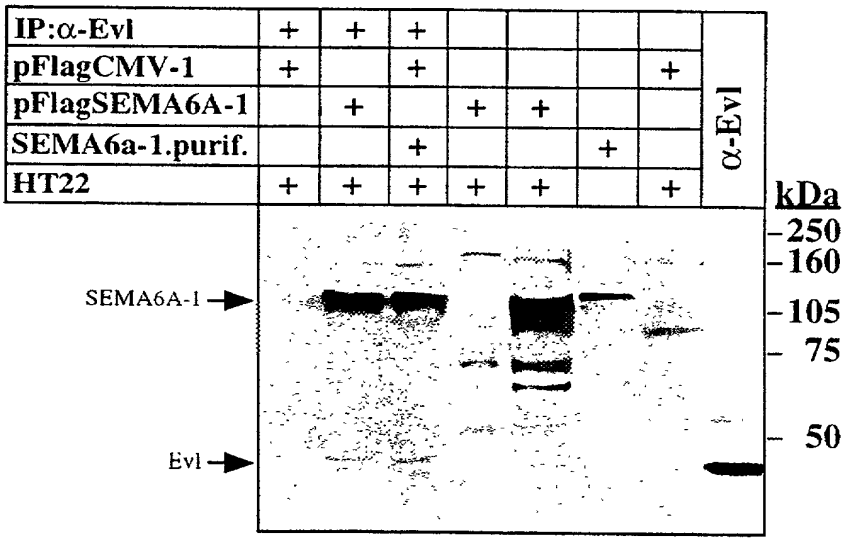
Fig. 6

Sequence-Alignment: SEMA6A-1 / Zyxin

```
SEMA6A-1                                                                (6a)
PPPAPQRVDSIQVHSSQPSGQAVTVSRQPSLNAYNSLTRSGLKRTPSLKPD-VPPKPSFAPLSTSMKPNDACT
* * ***   +* *  **  +   *  ** +++ *+  *  * + *+  *   *  * * *+ +   *
PPPQPQRKPQVQLH-VQPQAKP-HVQPQP-VSSANTQPRGPLSQAPTPAPKFAPVAPKFTPVVSKFSP
zyxin                                                                   (6b)
```

Identity: 33%
Similarity: 49%

A.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pFlagSEMA6A-1
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HT22
α-Evl
kDa
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160
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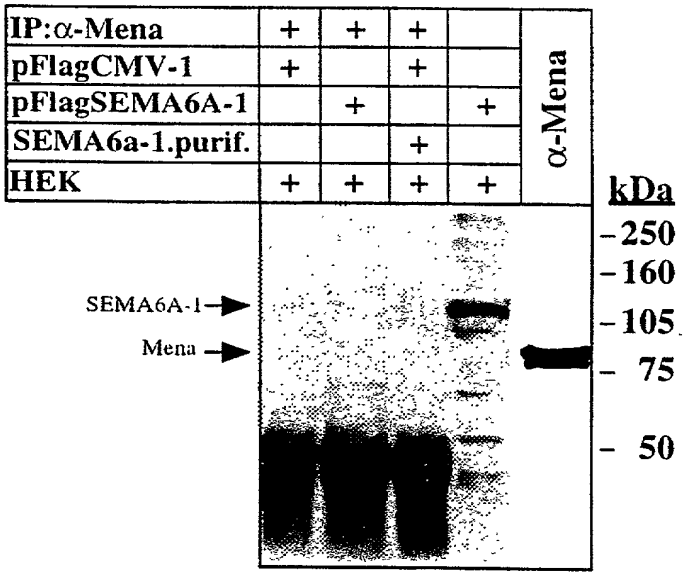
75
50
SEMA6A-1
Evl

B.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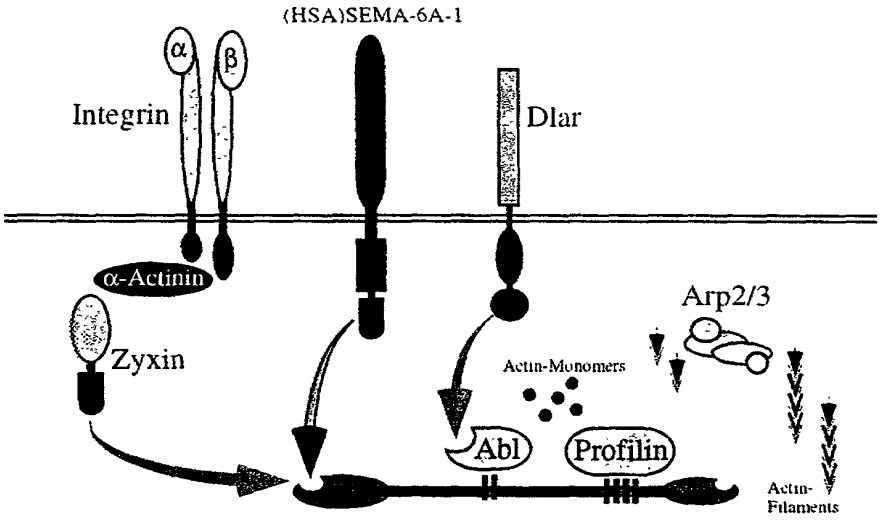
HEK
α-Mena
kDa
250
160
105
75
50
SEMA6A-1
Mena

Fig. 7

Fig. 8

From Membrane to Cytoskeleton: Enabling a Connection

(Hu and Reichardt, Neuron, Vol. 22; March 1999)



PATENTS #4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

BEHL, CHRISTIAN et al.

Serial No.: **09/856,681**
U. S. National Phase of PCT
EP 99/09215 Filed November 26, 1999

Filed: **May 22, 2001**

For: **HUMAN SEMAPHORIN 6A-1 (SEMA6A-A), A GENE INVOLVED IN NEURONAL DEVELOPMENT AND REGENERATION MECHANISMS DURING APOPTOSIS, AND ITS USE AS A POTENTIAL DRUG TARGET**

NOTICE OF CHANGE OF ADDRESS

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please address all future correspondence in this matter to:

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I hereby certify that this correspondence is being deposited with the United States Postal Service as **Express Mail No. EL602997982US** in an envelope addressed to: Commissioner of Patents and Trademarks, Box PCT, Washington, DC, 20231, on **August 3, 2001**.

John K. McDonald - Reg. No. 42,860

Respectfully submitted,

By: John K. McDonald, Ph.D.

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Suite 2800
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Atlanta, Georgia 30309-4530
Docket: 48498-258443

#3

DECLARATION AND POWER OF ATTORNEY

Attorney's Docket No. **48498-258443**

In re Application of: **BEHL, Christian, et al.**
As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **HUMAN SEMAPHORIN 6A-1 (SEMA6A-A), A GENE INVOLVED IN NEURONAL DEVELOPMENT AND REGENERATION MECHANISMS DURING APOPTOSIS, AND ITS USE AS A POTENTIAL DRUG TARGET**, the specification of which:

☐ is attached hereto.
☒ was filed on May 22, 2001, as Application No. 09/856,681.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I do not know and do not believe that the same was ever known or used by others in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to the date of this application. I further state that the invention was not in public use or on sale in the United States of America more than one year prior to the date of this application. *I understand that I have a duty of candor and good faith toward the Patent and Trademark Office,* and I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of the foreign application(s) for patent or inventor's certificate listed below, and have also identified below any foreign application for patent or inventor's certificate disclosing subject matter in common with the above-identified specification and having a filing date before that of the application on which priority is claimed:

Application No.	Country	Filing Date	Priority Claimed Under 35 USC §119	
98 122 441.3	EP	November 26, 1998	Yes X	No
PCT/EP99/09215	PCT	November 26, 1999	Yes X	No

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statement were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

POWER OF ATTORNEY: The following attorneys are hereby appointed to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: **Customer Number 23594**

Direct all correspondence to: **Customer Number 23594**

Direct telephone calls at **404-949-3999**, to **John K. McDonald, Ph.D.**

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23594
PATENT TRADEMARK OFFICE

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Inventor's signature X	Date: X 21.06.01
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Inventor's signature X	Date: X 20/6/01
Residence and Post Office Address: **Parsbergerstraße 3, 81249 München, DE** DEX	

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